Modulo 1 - Flogosi e metabolismo

LA FLOGOSI COME FATTORE FAVORENTE DI PATOLOGIE CARDIOVASCOLARI

Andrea Benso
SCDU Endocrinologia, Diabetologia e Metabolismo
Dipartimento di Scienze Mediche
Università di Torino

e-mail: andrea.benso@unito.it

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DI TORINO

La flogosi come fattore favorente di patologie cardiovascolari

- ✓ Il processo aterosclerotico: l'era della "inflammatory hypothesis"
- ✓ La valutazione dello "stato infiammatorio" in relazione al rischio CV
- ✓ I trial clinici
- ✓ Cosa succede nella pratica clinica

- ✓ **Il processo aterosclerotico: l'era della "inflammatory hypothesis"**
- ✓ La valutazione dello "stato infiammatorio" in relazione al rischio CV
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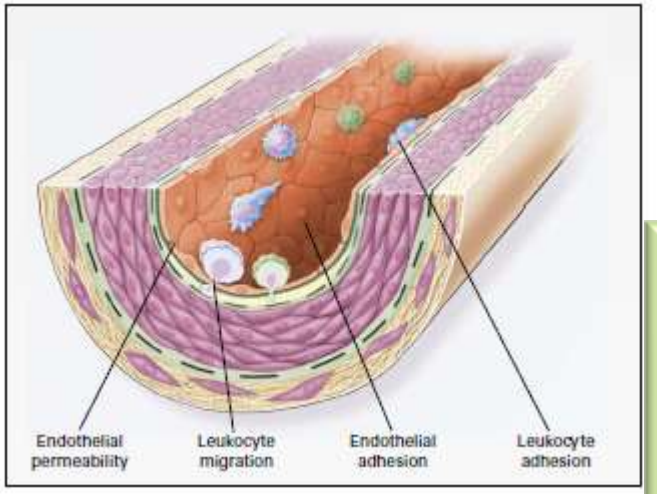
"Atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate and activate lesions in the arterial tree"
[Hansson, NEJM 2005]

The NEW ENGLAND JOURNAL of MEDICINE

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

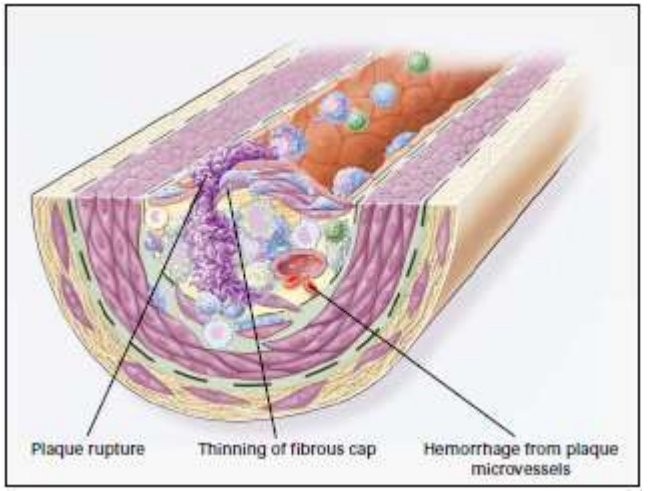
1999;340:115-26

RUSSELL ROSS, PH.D.

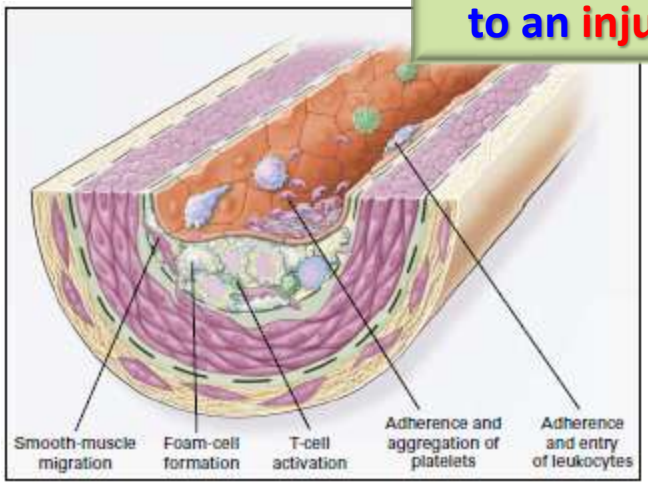


Endothelial Dysfunction in Atherosclerosis

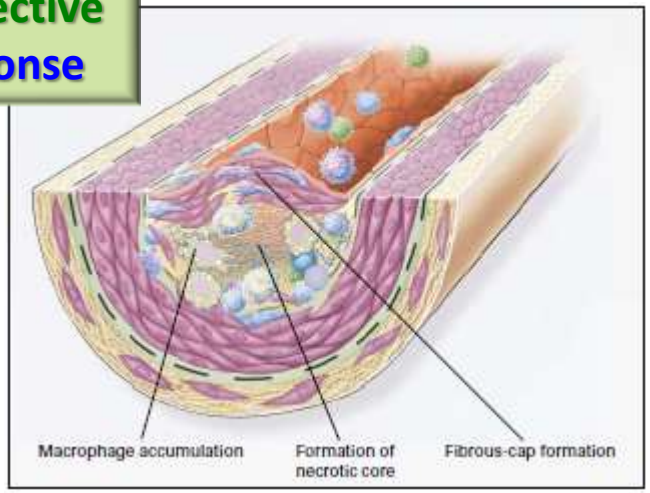
..if the injurious agents are not removed or nullified by the inflammatory response and the inflammation progress, **the response changes from a protective to an injurious response**



Unstable Fibrous Plaques in Atherosclerosis

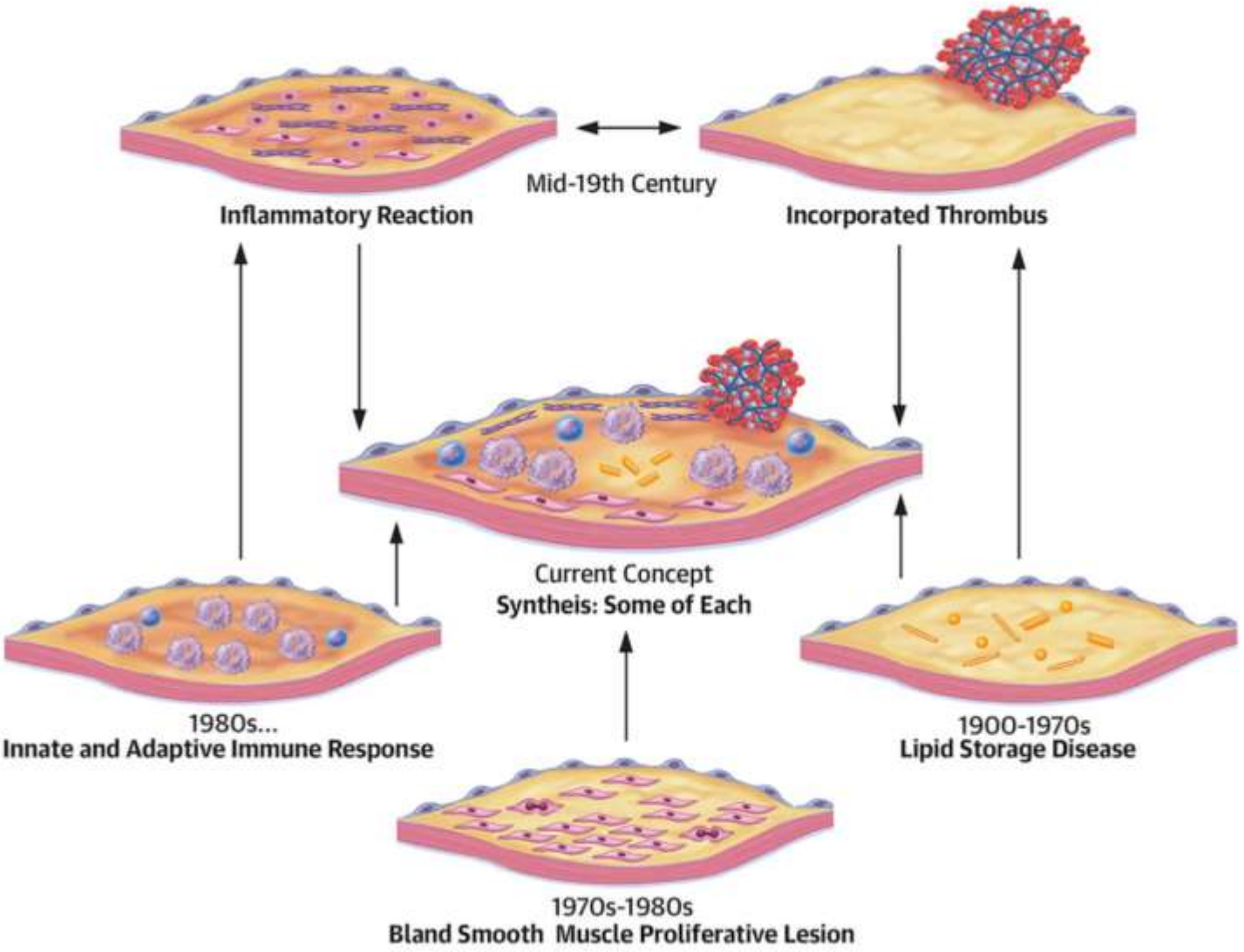


Fatty-Streak Formation in Atherosclerosis



Formation of an Advanced, Complicated Lesion of Atherosclerosis

Evolution of the concepts of the pathogenesis of atherosclerosis



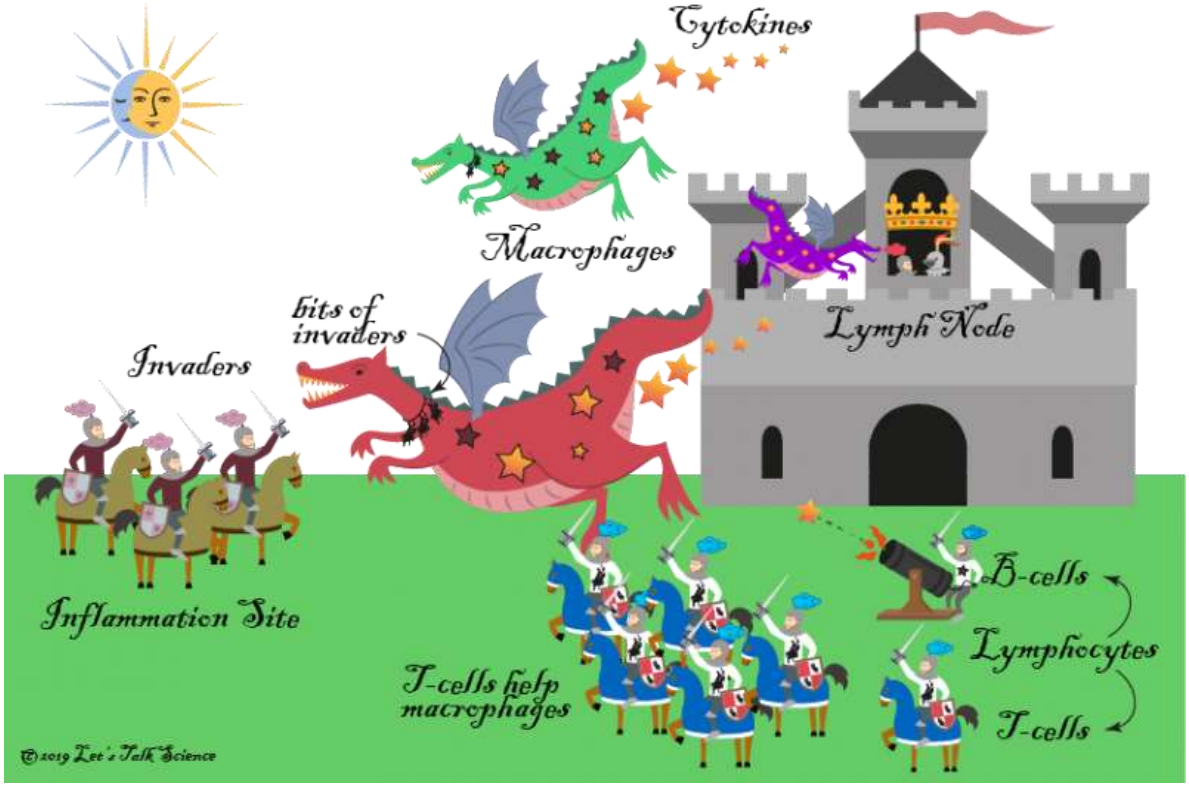
Libby & Hansson, *J Am Coll Cardiol* 2019

The **INNATE** immune response

✓mounts **rapidly**

✓combats perceived foreign invaders, often with **preformed mediators**

✓is characterized as **"fast and blunt"**, recognizes a limited diversity of structures on the order of **hundreds**

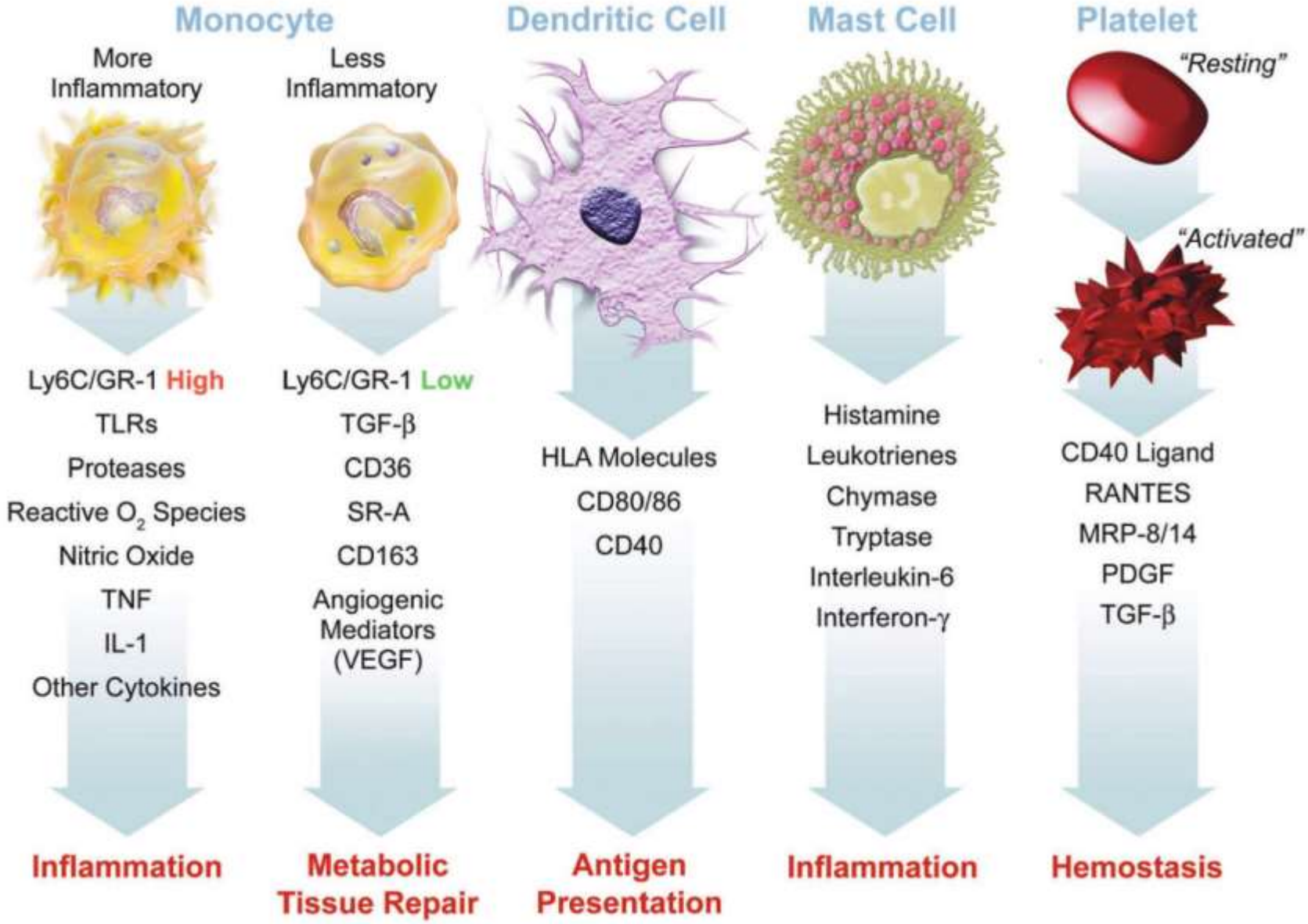


The **ADAPTIVE** immune response (in contrast to the innate immune response)

✓ requires **"education"** of the immune system

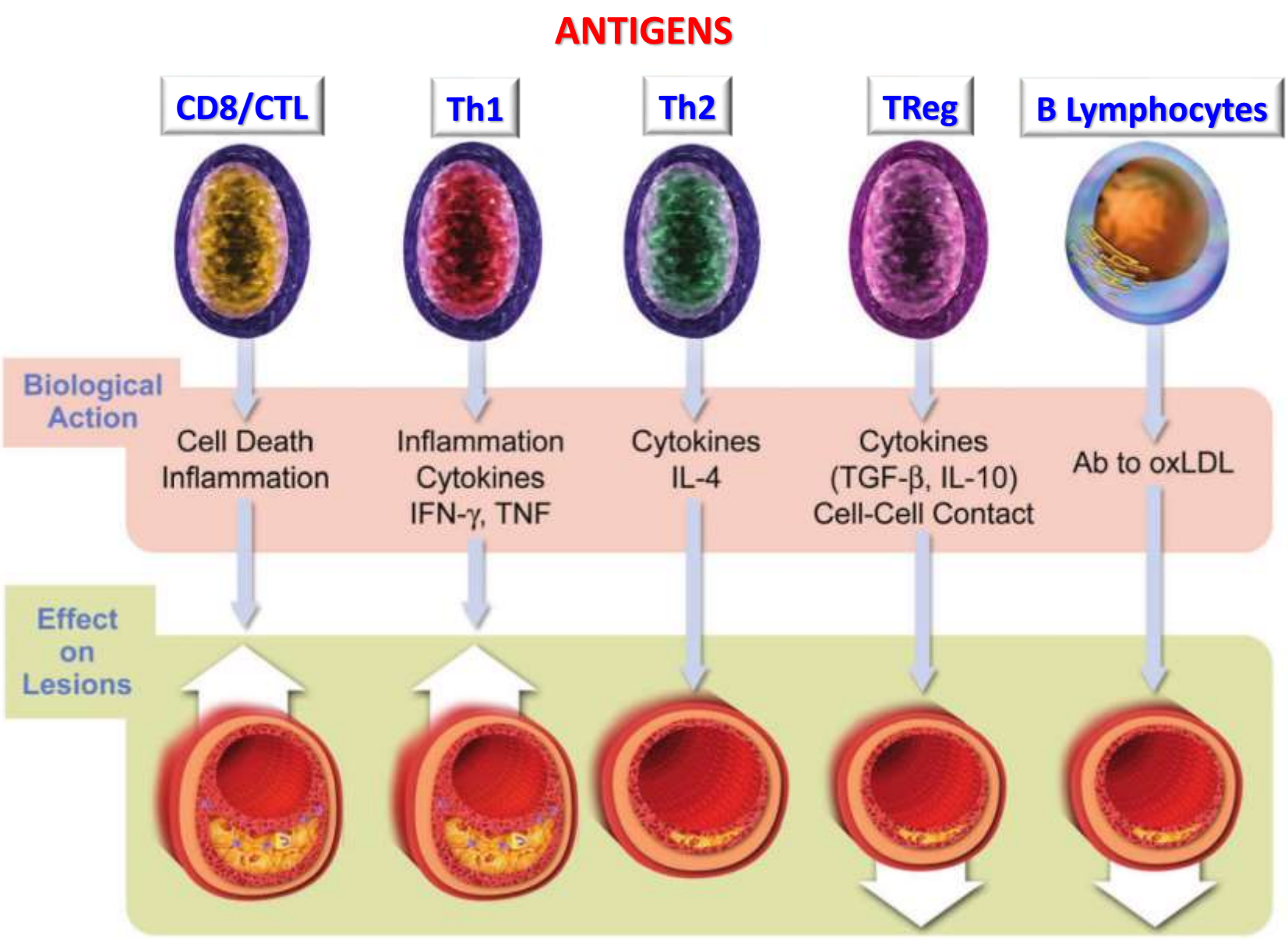
✓ the repertoire of Ab and T cell receptors can recognize many **millions** of specific structures.

Elements involved in INNATE immunity



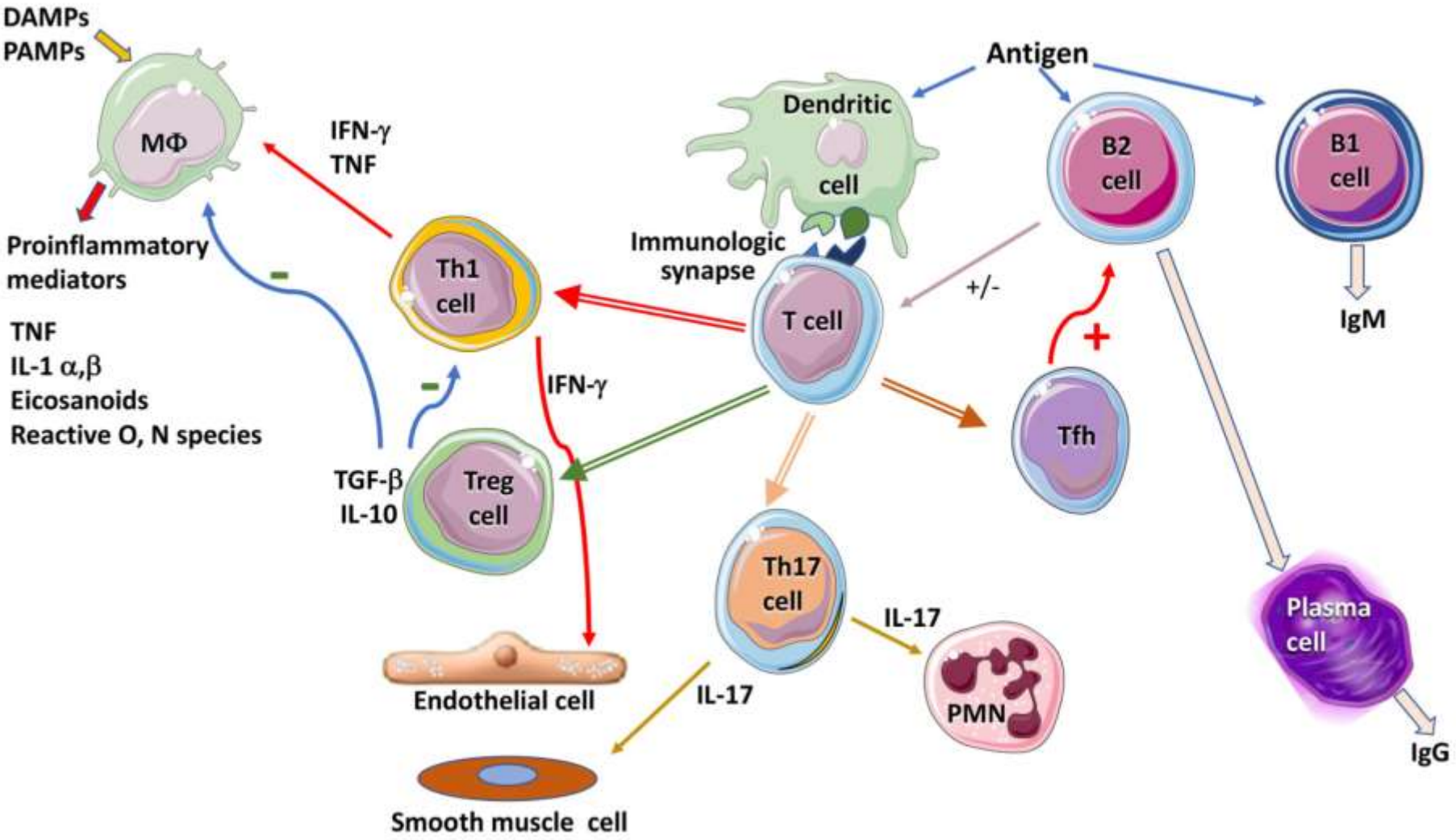
Libby et al., *J Am Coll Cardiol* 2009

Elements involved in ADAPTIVE immunity



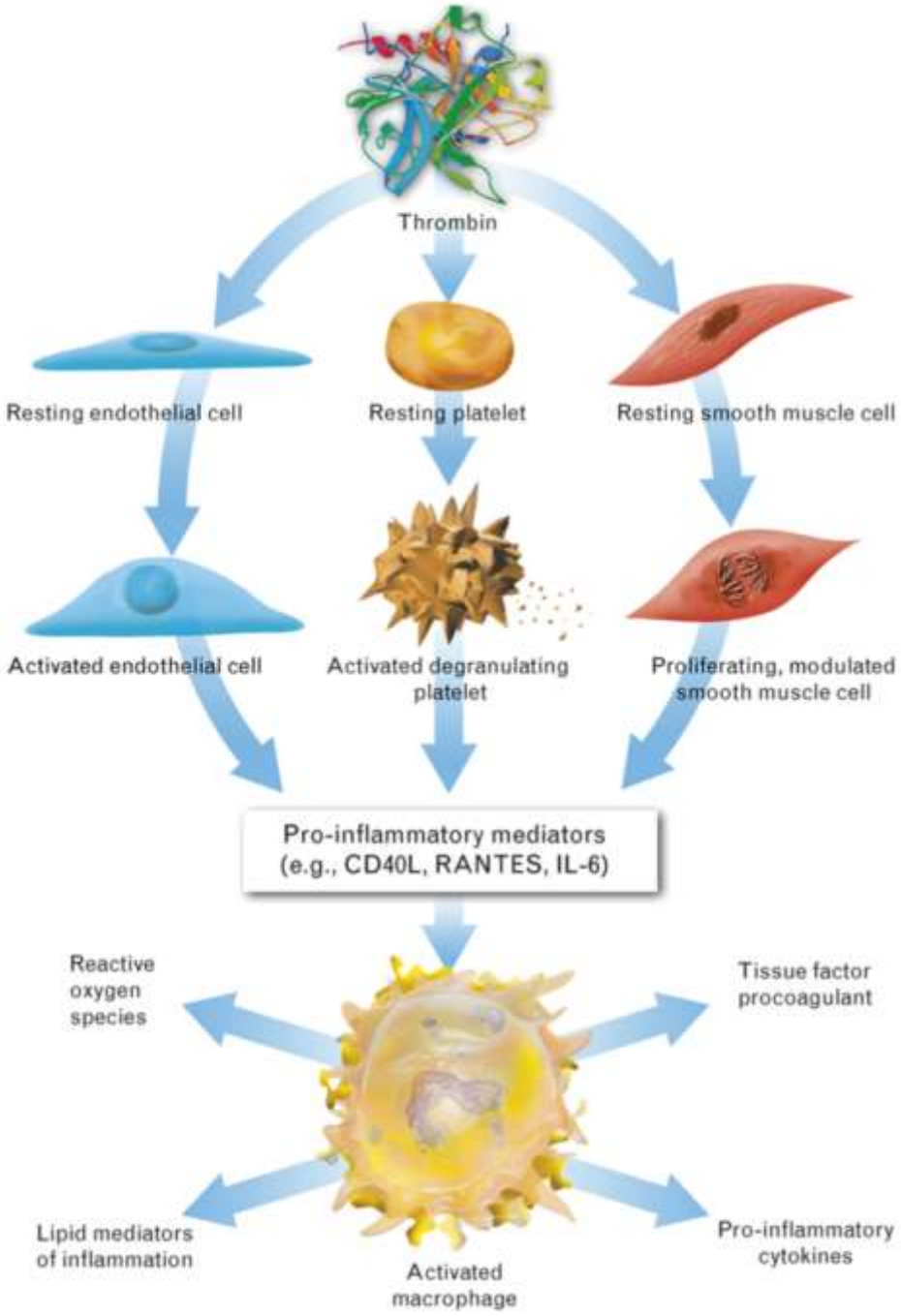
Libby et al., *J Am Coll Cardiol* 2009

A simplified view of the operation of innate and adaptive immunity as thought to operate in atherogenesis



Libby & Hansson, *J Am Coll Cardiol* 2019

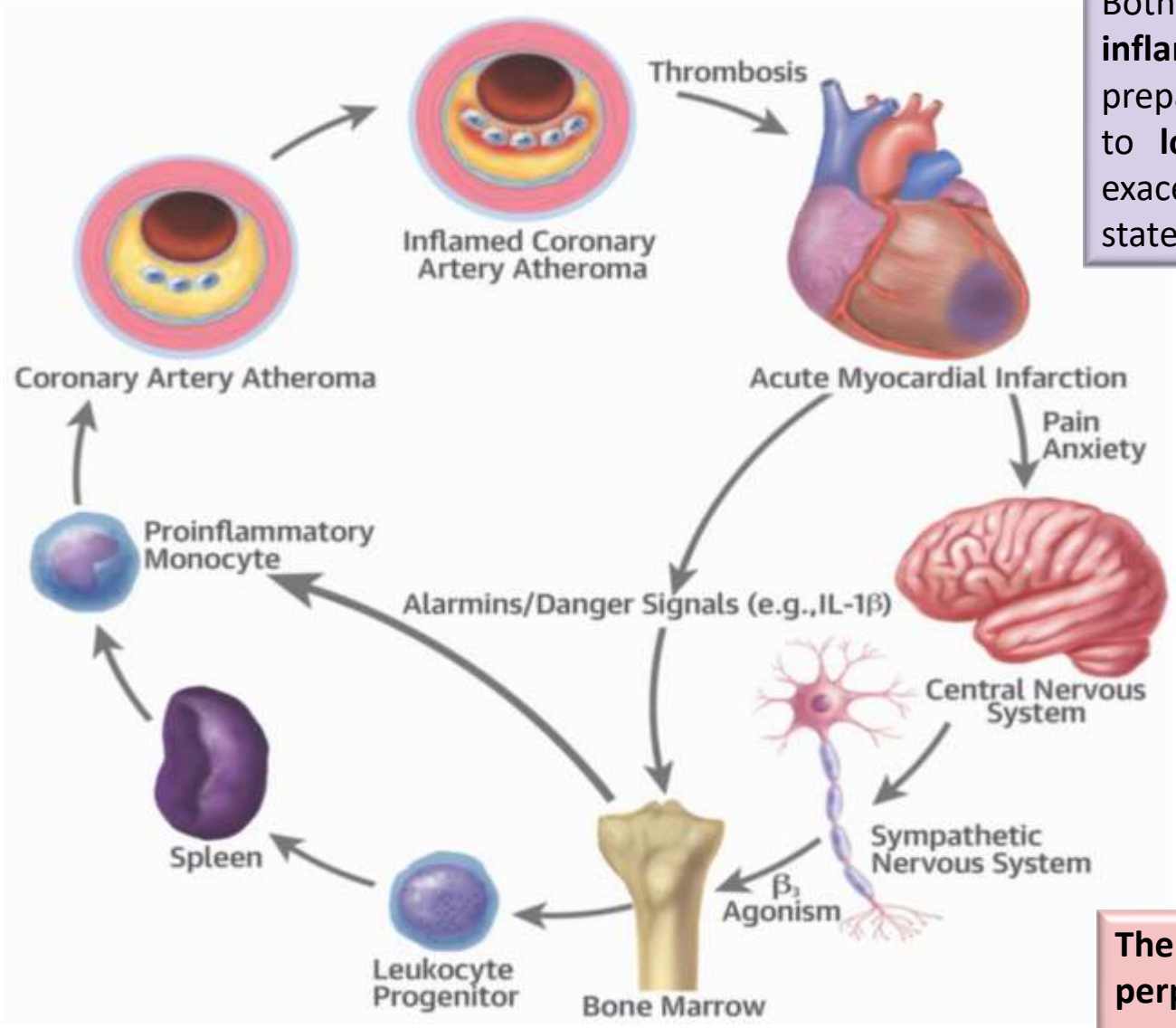
Thrombosis begets inflammation



Platelets not only contribute to thrombus formation but, **when activated**, also **release pre-formed proinflammatory mediators** from their granules

Libby & Hansson, *J Am Coll Cardiol* 2019

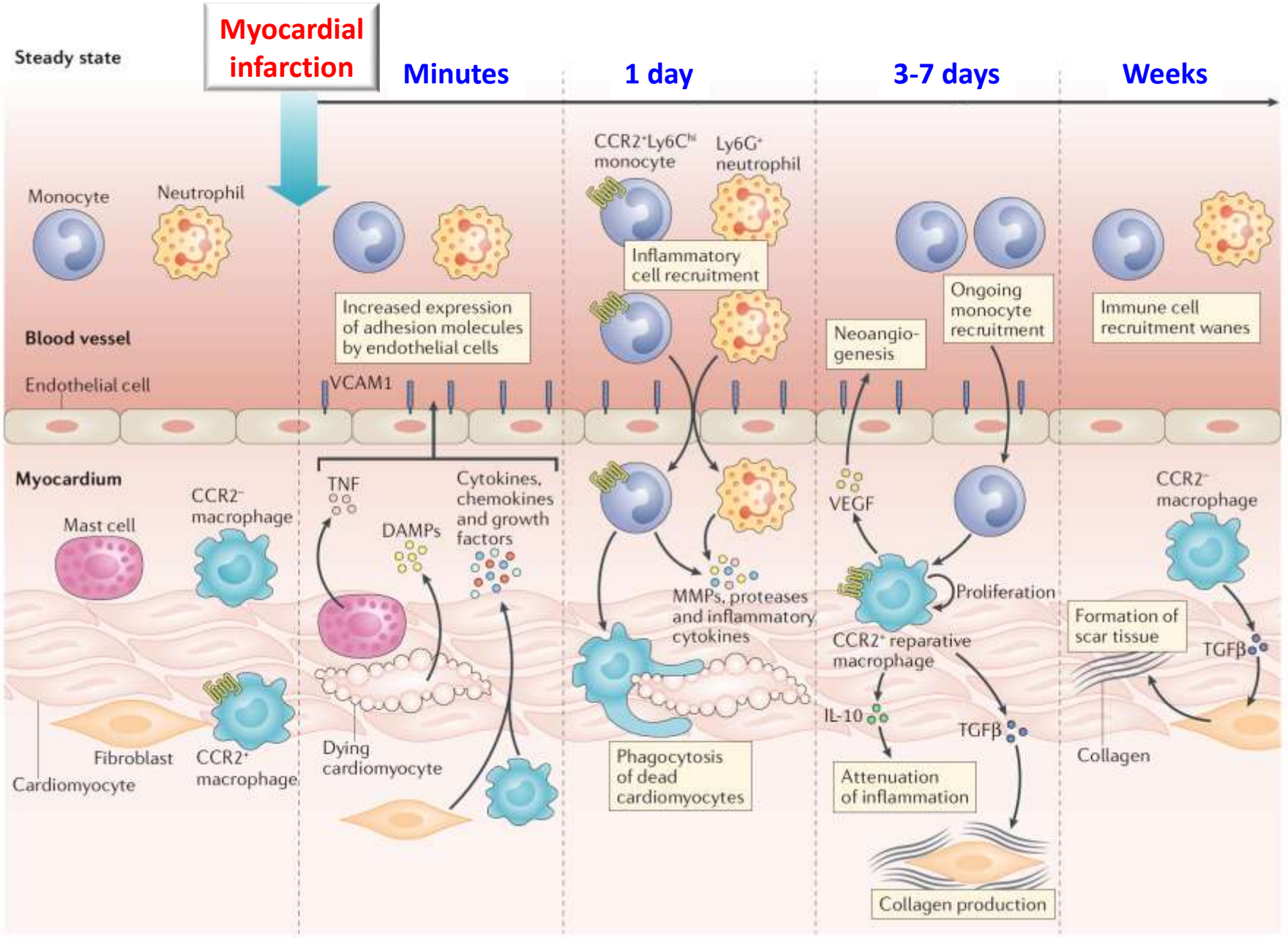
The expanded cardiovascular continuum



Both **systemic** and **local** **inflammation** can impinge on the prepared soil of the plaque leading to **local inflammatory activation** exacerbating the inflammatory state.

The cycle of inflammation can perpetuate leading to recurrent events and aggravated atherothrombosis

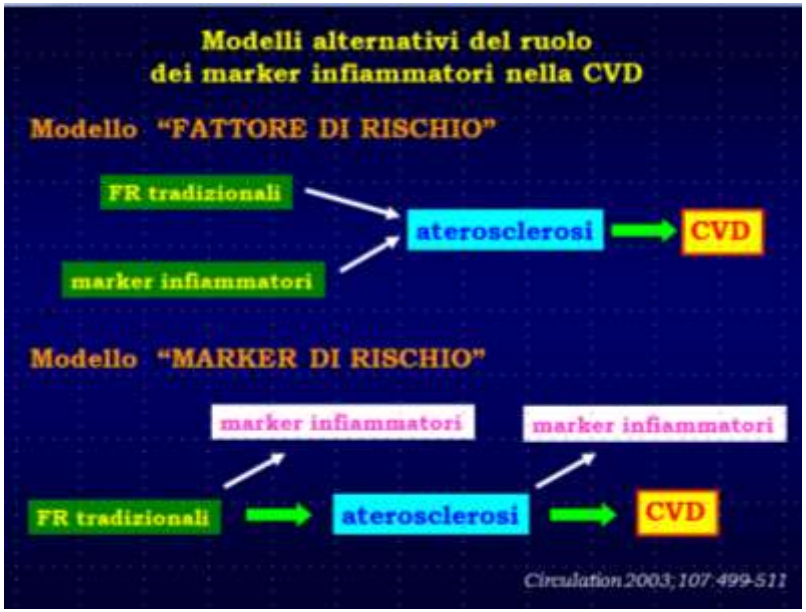
Libby & Hansson, *J Am Coll Cardiol* 2019



Swirski & Nahrendorf, *Nat Rev Immunol* 2018

La flogosi come fattore favorente di patologie cardiovascolari

- ✓ Il processo aterosclerotico: l'era della "inflammatory hypothesis"
- ✓ **La valutazione dello "stato infiammatorio" in relazione al rischio CV**
- ✓ I trial clinici
- ✓ Cosa succede nella pratica clinica



The **clinical utility** of a biomarker for risk prediction depends on

✓ praticability, ease, cost and reproducibility of the measurement

✓ the ability **to add** the predicability of existing biomarkers

Biomarkers of inflammation proposed for **diagnostic use**:

- myeloperoxidase
- lipoprotein-associated phospholipase A2 (Lp-PLA2)
- pentraxin-3
- IL-6, IL-8
- matrix metalloproteinase 9
- hs-CRP
- VCAM-1
- ICAM-1
- P-selectin
- levels of circulating CD14+, CD16++ and CD16+ monocytes
- neopterin, pregnancy-associated plasma protein-A

hs-CRP

Libby et al., *J Am Coll Cardiol* 2009
Ruparelia & Choudhury, *Heart* 2020

hsCRP is **strongly associated** with incident **myocardial infarction**, **stroke**, and **cardiovascular death**, both in **primary** and in **secondary** prevention, **indipendent of established risk factors**.

Libby et al., *J Am Coll Cardiol* 2009

Clinical Application of C-Reactive Protein for Caerdiovascular Disease Detection and Prevention

Ridker PM

Circulation 2003;107:363-9

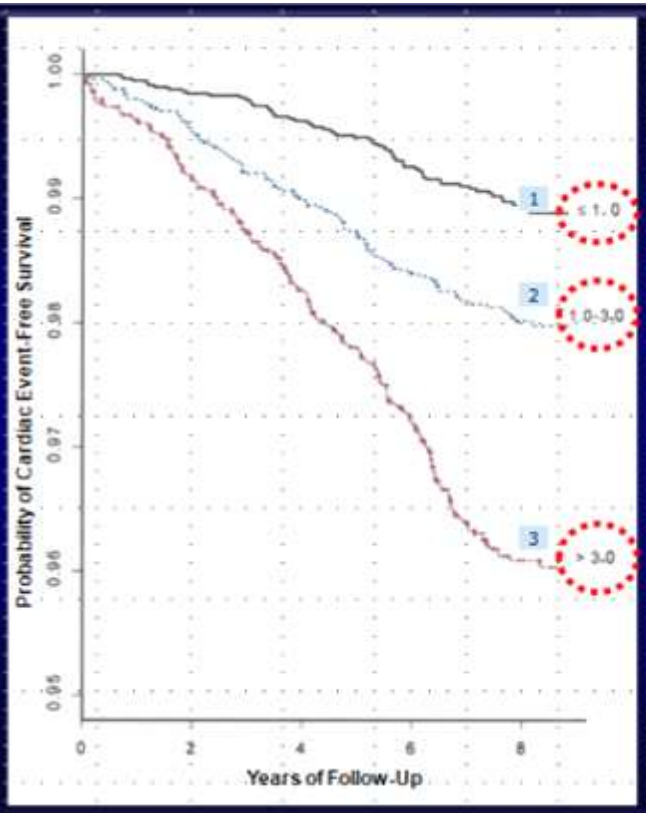
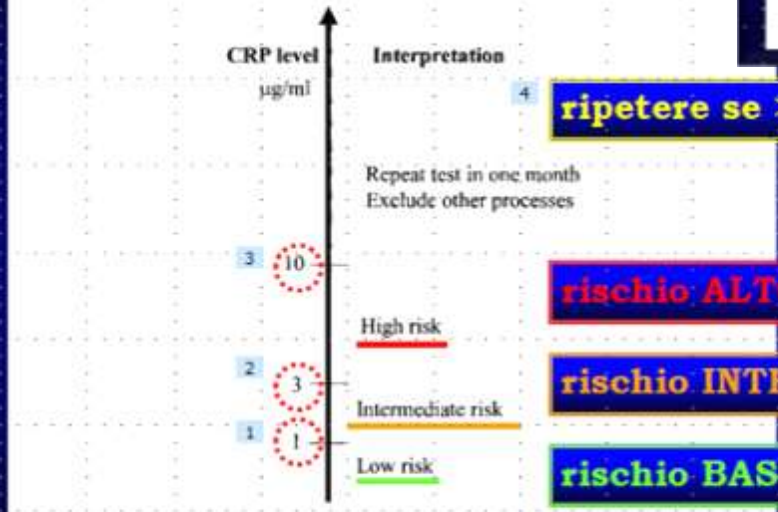


Fig.2 Cardiovascular event-free survival among **apparently healthy** individuals according to baseline CRP levels

Coming of Age of C-Reactive Protein

Yeh ETH et al.



CRP level and cardiovascular risk. CRP levels are listed on the left and interpretations are on the right.

Circulation 2003;107:370-2

hsCRP

✓ is a protein made by the **liver**

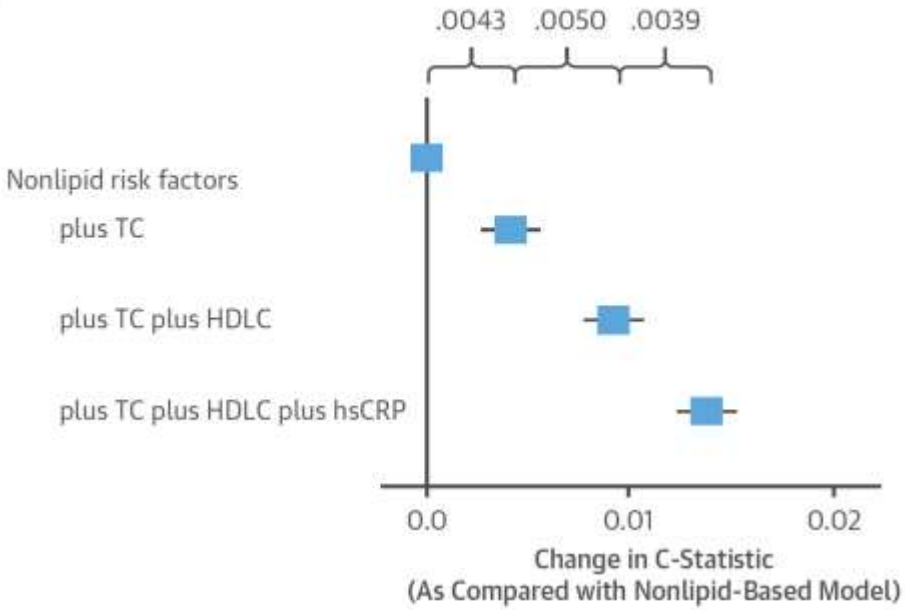
✓ is **NOT the causal pathway** for atherogenesis

✓ is **largely uninformative** about the precise nature of upstream drivers

Ruparelia & Choudhury, *Heart* 2020

Clinical utility of risk prediction and stability over time of hsCRP are virtually identical to those of LDL-c

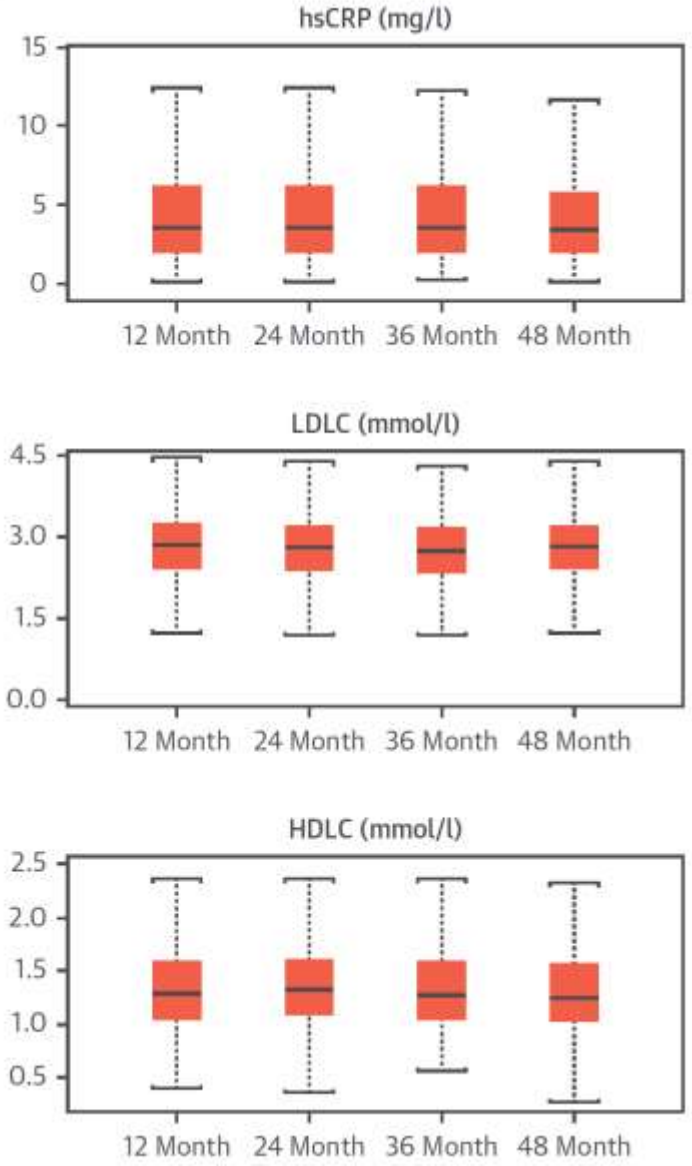
A



B **8901 subjects over a 4-year period**

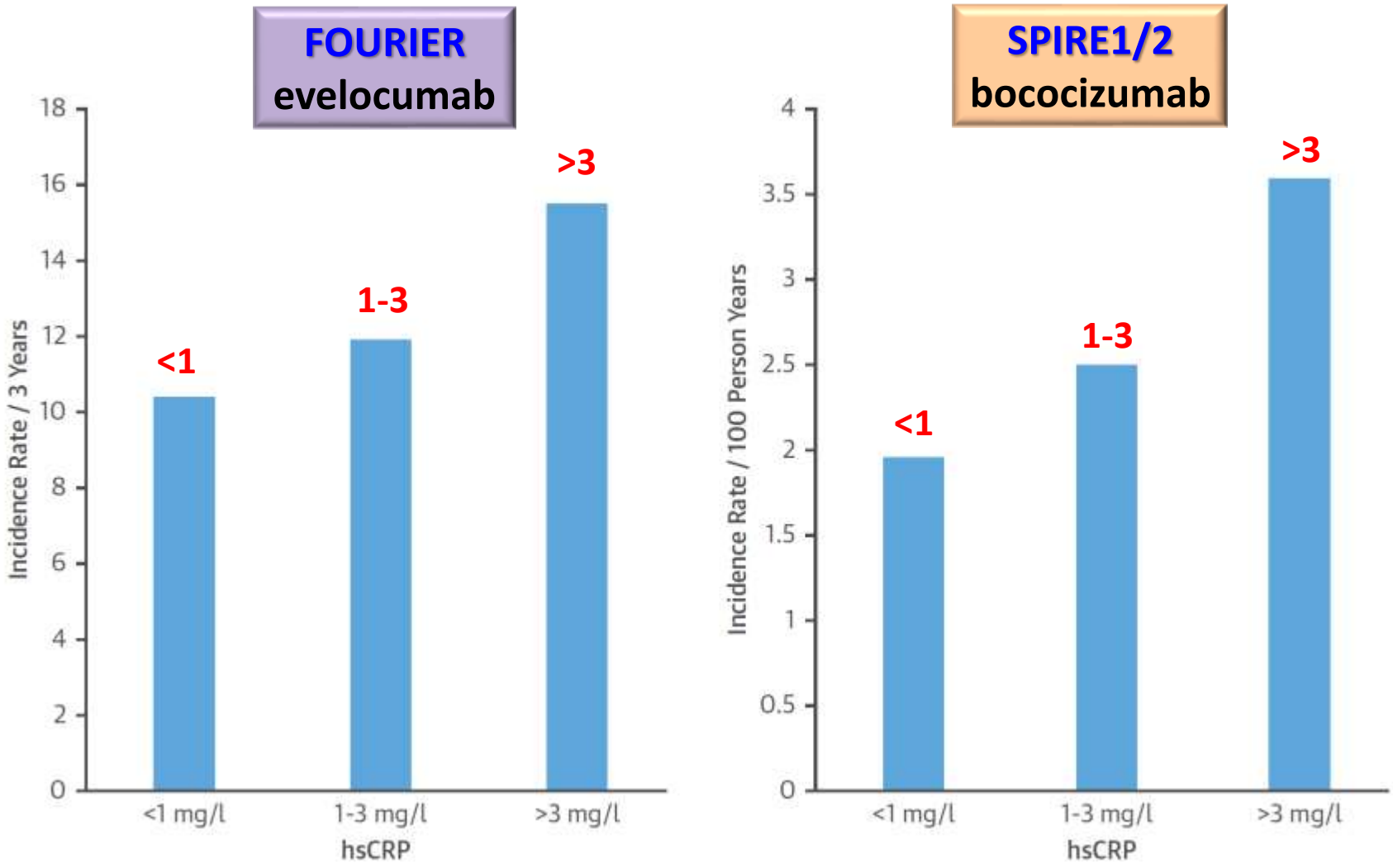
Variable	Intra-Class Correlation	95% CI
hsCRP	0.54	0.53-0.55
LDLC	0.57	0.56-0.58
BP (systolic)	0.49	0.43-0.54
BP (diastolic)	0.41	0.38-0.43

C



Ridker, *J Am Coll Cardiol* 2018

Residual inflammatory risk is present even after maximal possible LDL-c lowering



Incidence rates of major cardiovascular events according to hsCRP levels among high-risk patients already treated with statins and PCSK-9 inhibitors

Ridker, *J Am Coll Cardiol* 2018

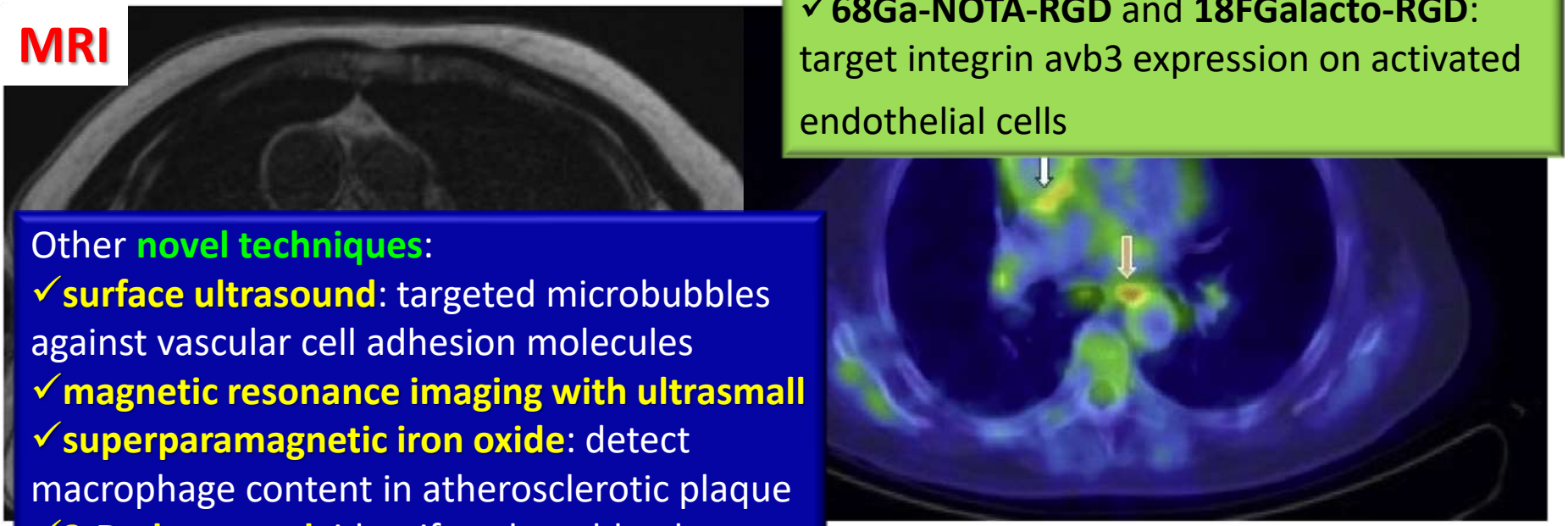
Imaging biomarkers

Positron emission tomography (PET) is increasingly being used for the **assessment of arterial inflammation** and to test the efficacy of therapeutic interventions aimed at reducing inflammation and thus atherosclerosis progression.

Novel PET tracers:

- ✓**68Ga-DOTATATE**: links to SST-R 2 in macrophages and damaged endothelial cells
- ✓**11C-PK11195**: targets activated macrophages translocator protein receptors
- ✓**18F-FMCH**: targets macrophage cell membranes
- ✓**68Ga-NOTA-RGD** and **18FGalacto-RGD**: target integrin avb3 expression on activated endothelial cells

MRI



Other **novel techniques**:

- ✓**surface ultrasound**: targeted microbubbles against vascular cell adhesion molecules
- ✓**magnetic resonance imaging with ultrasmall**
- ✓**superparamagnetic iron oxide**: detect macrophage content in atherosclerotic plaque
- ✓**3-D ultrasound**: identify vulnerable plaques in carotid
- ✓**18F-sodium fluoride PET**: identify vulnerable plaques in coronary arteries

shows FDG uptake both in the ascending and descending aorta, suggesting the **presence of inflammatory infiltrates in the vessel wall**

Raggi et al., *Atherosclerosis* 2018

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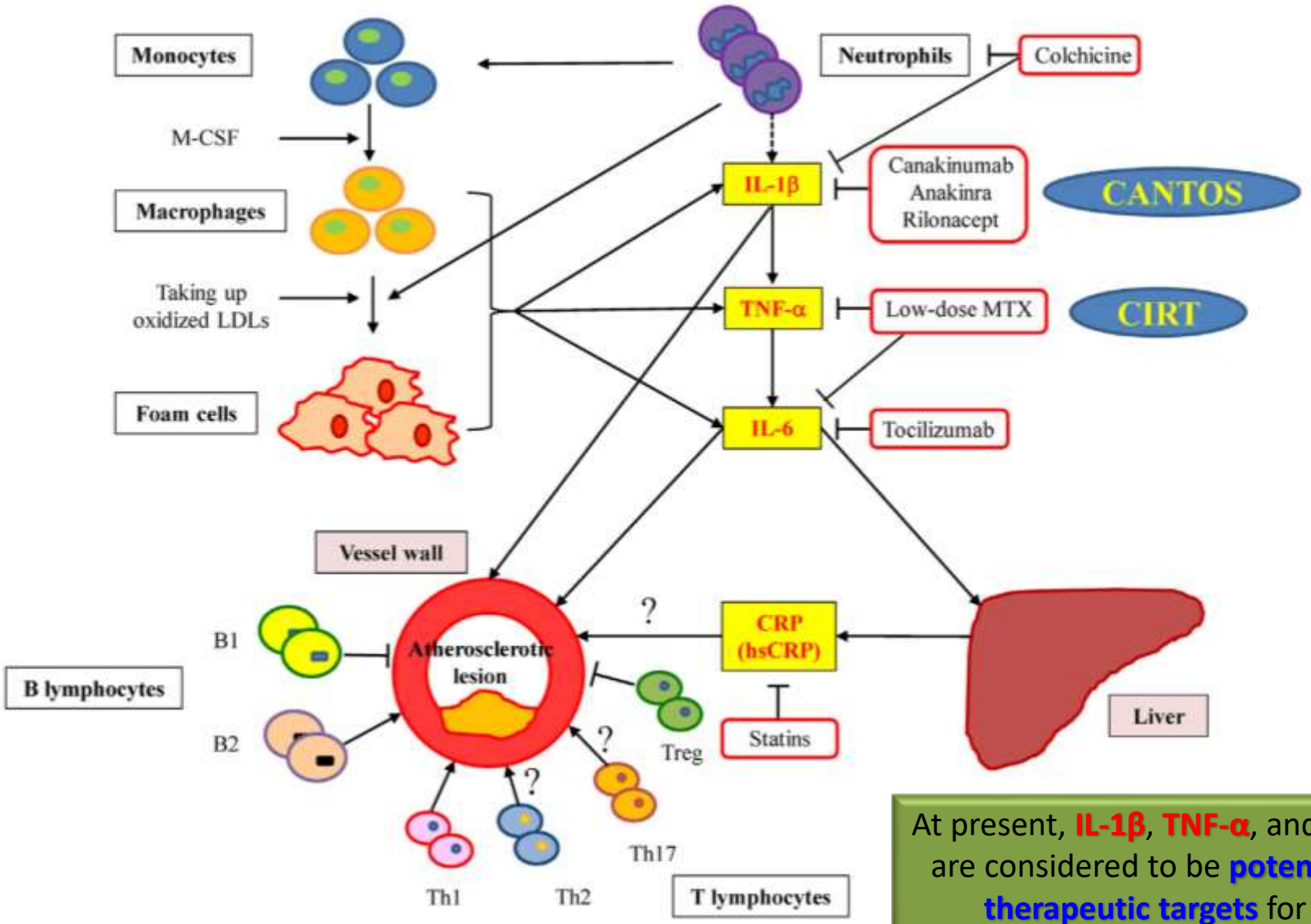
Schematic representation of mechanisms and potential targets of inflammation in atherosclerosis.

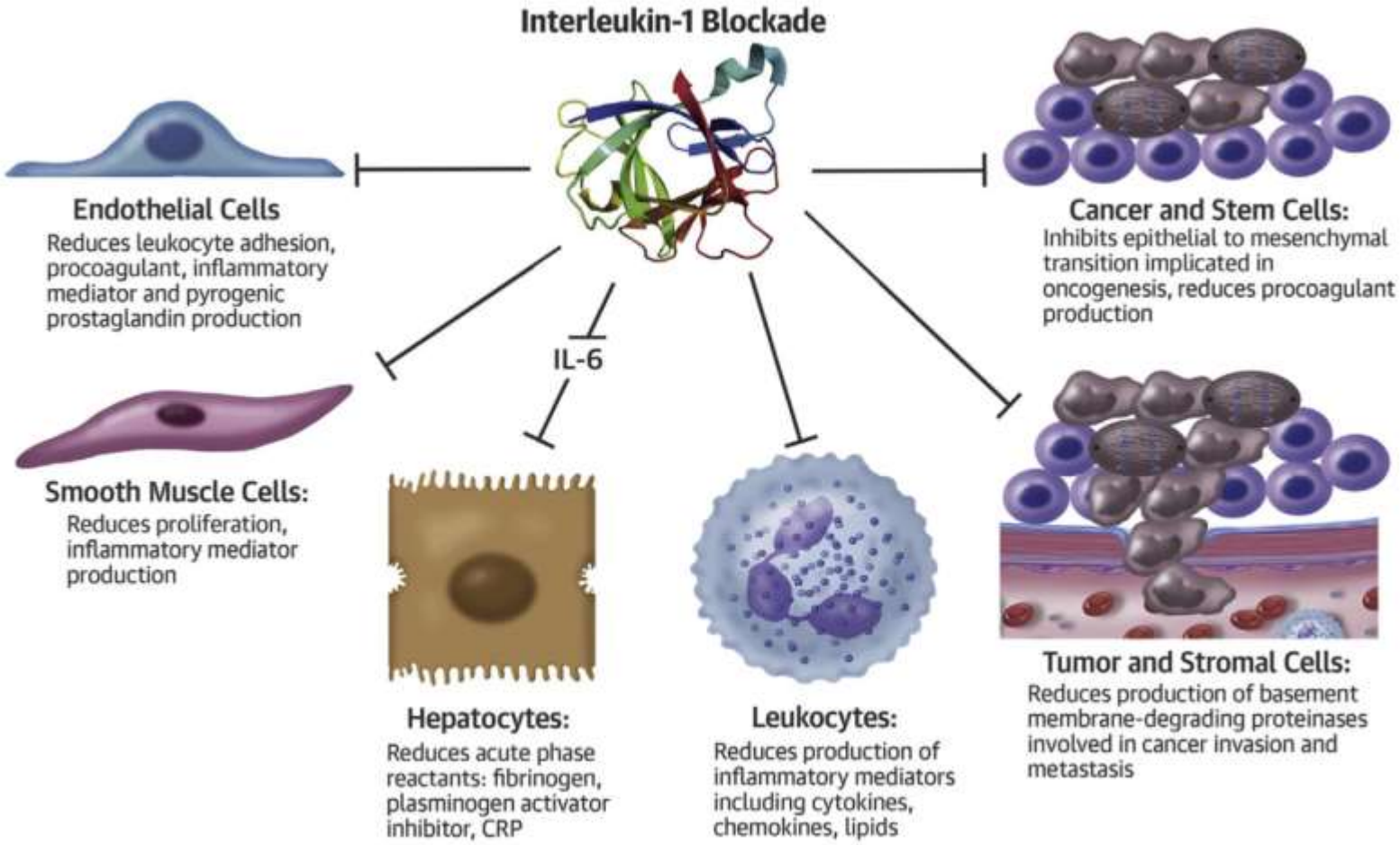


At present, **IL-1β**, **TNF-α**, and **IL-6** are considered to be **potential therapeutic targets** for atherosclerosis.

Moriya, *J Cardiol* 2019

Clinical trials of inflammation modulation in the atherosclerotic cardiovascular disease

Schematic representation of the contribution of interleukin 1β to the inflammatory cascade and potential benefits of its blockade



Raggi et al., *Atherosclerosis* 2018

The NEW ENGLAND JOURNAL of MEDICINE

2017
377:1119-31

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

CANTOS Trial

10.061 patients with
previous myocardial infarction AND hsCRP ≥2 mg/l

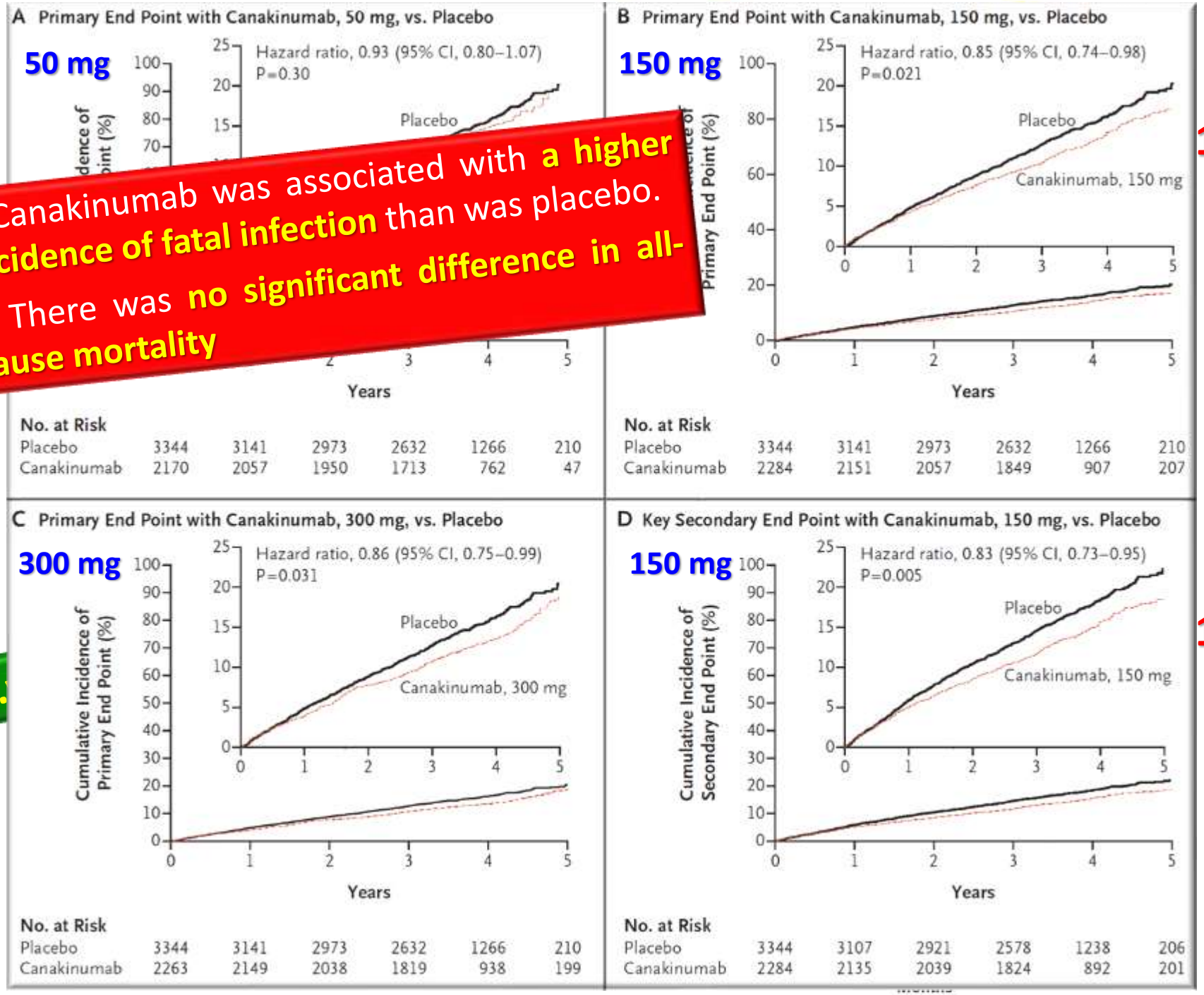
Canakinumab: **50** mg, **150** mg and **300** mg (administered s.c. every 3 m)
vs **placebo**

Median follow-up: **3.7 years**

Primary efficacy end point:

- ✓ **nonfatal myocardial infarction**
- ✓ **nonfatal stroke**
- ✓ **cardiovascular death**

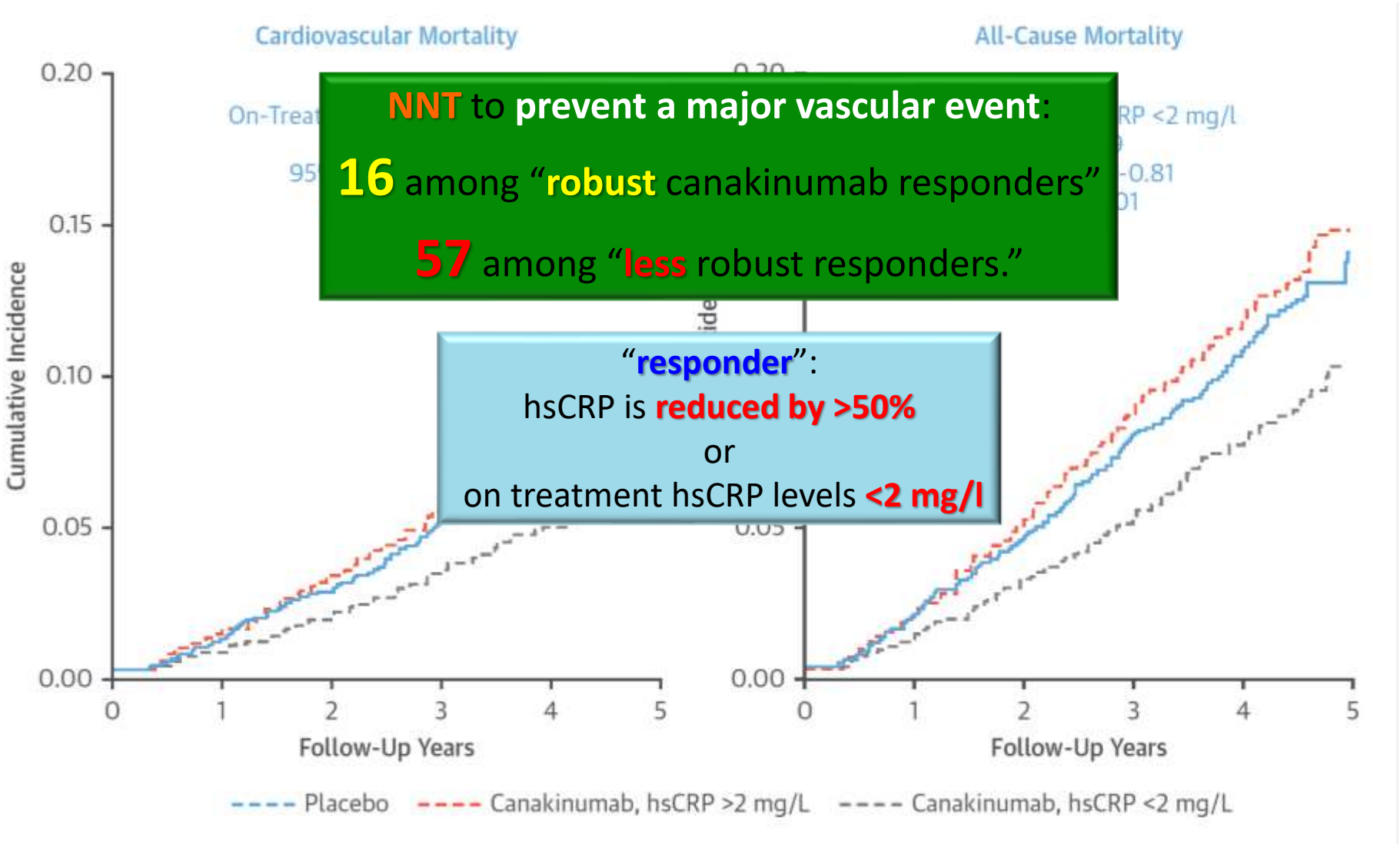
Secondary: **Primary + hospitalization for unstable angina that led to urgent revascularization**



Ridker et al., *NEJM* 2017

Greater risk reductions in CANTOS with greater hsCRP reduction

[including 31% RR reductions in CV mortality and all-cause mortality]



Ridker, *J Am Coll Cardiol* 2018

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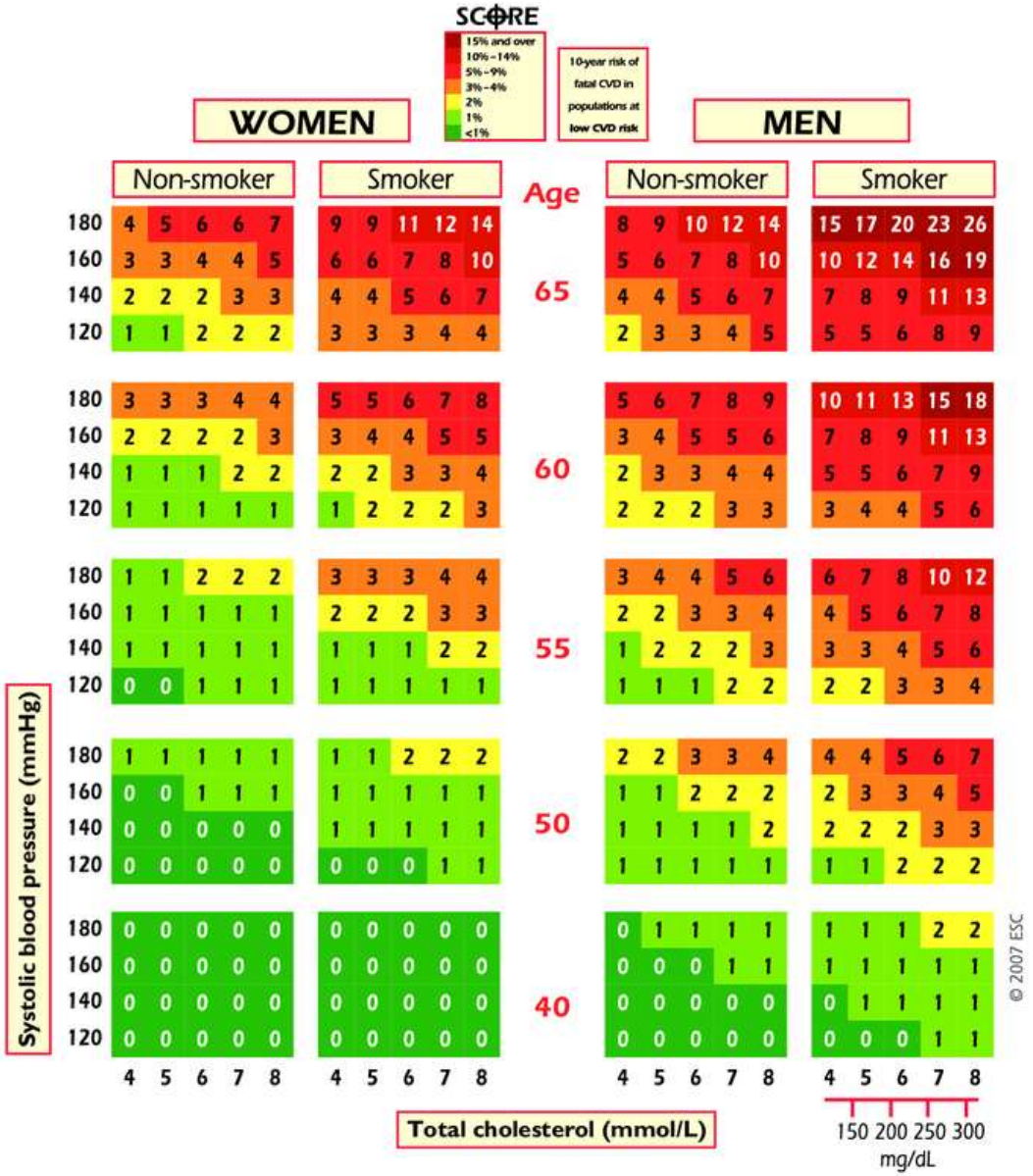
Stratificazione del rischio cardiovascolare

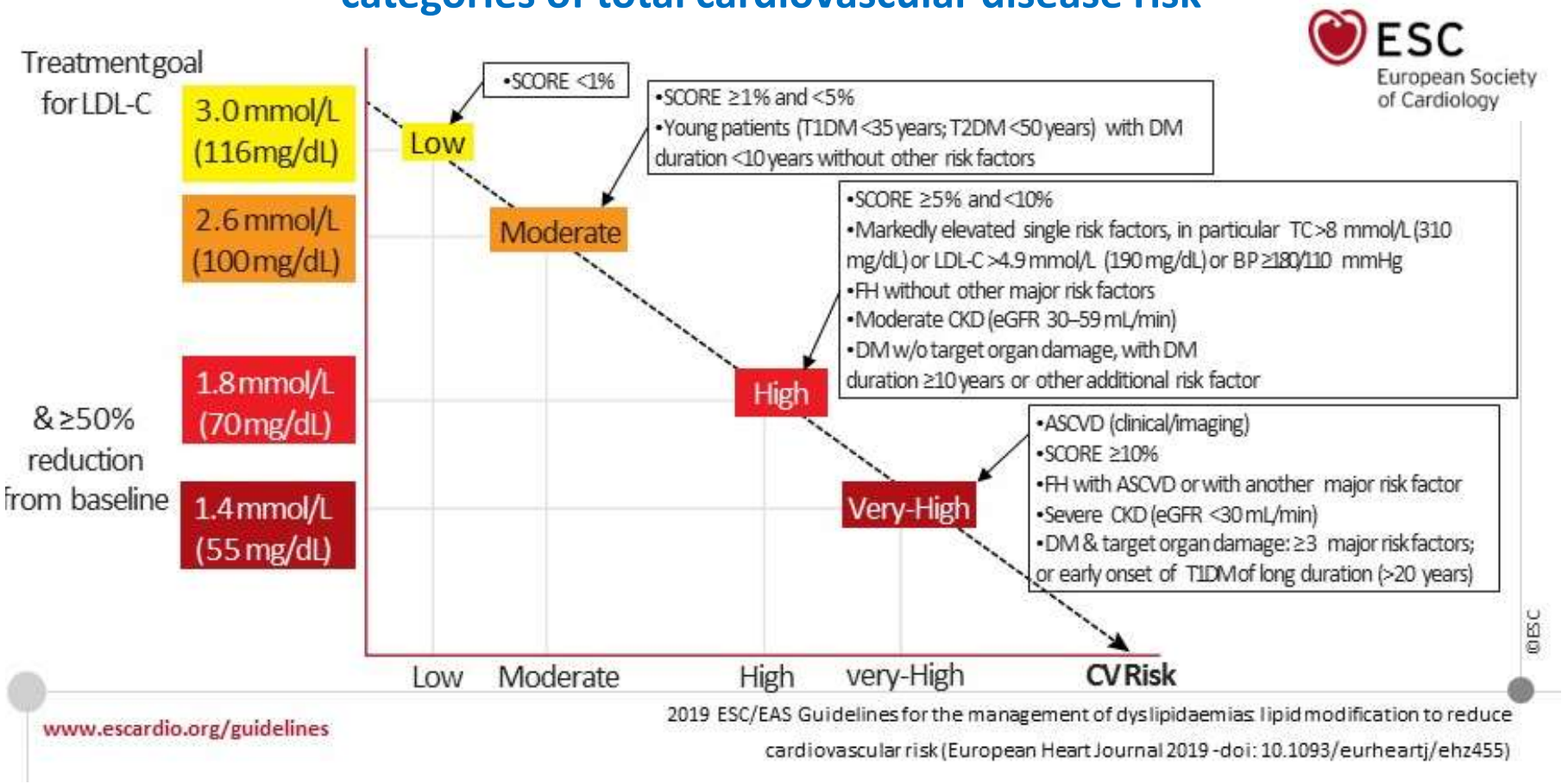


Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

Genere
Fumo
Età
Colesterolo totale
Pressione sistolica

Sedentarietà
Col-HDL
Obesità
Familiarità per CVD precoce
Stato infiammatorio
Malattie infiammatorie
….

Treatment goals for low-density lipoprotein across categories of total cardiovascular disease risk



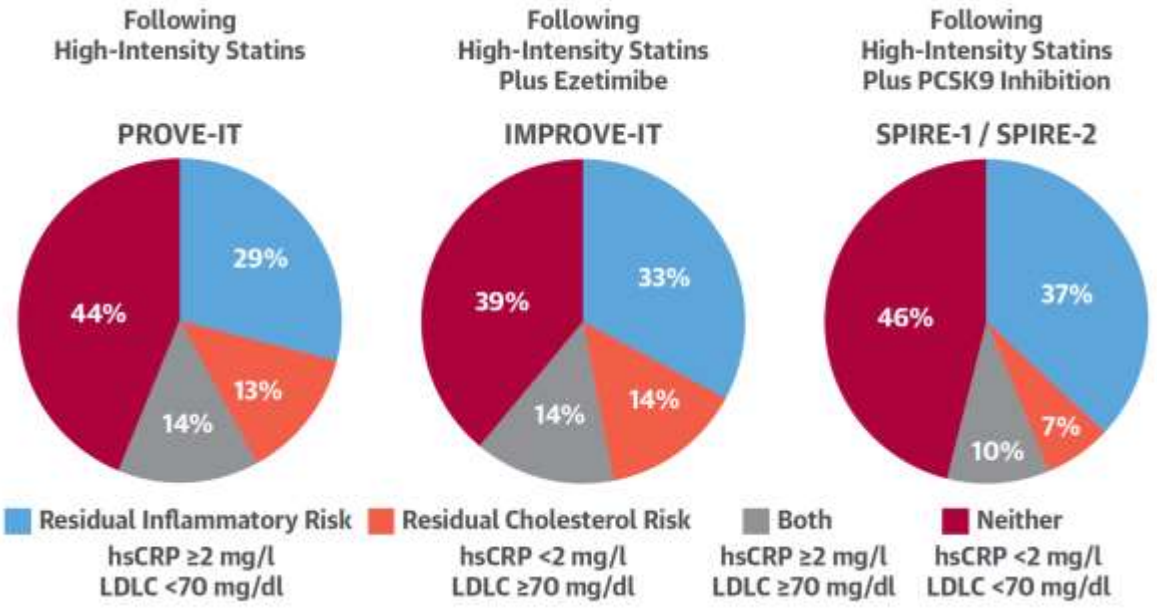
180	1	1	2	2	2
160	1	1	1	1	1
140	1	1	1	1	1
120	0	0	1	1	1

Donna 55 anni

Non fumatrice

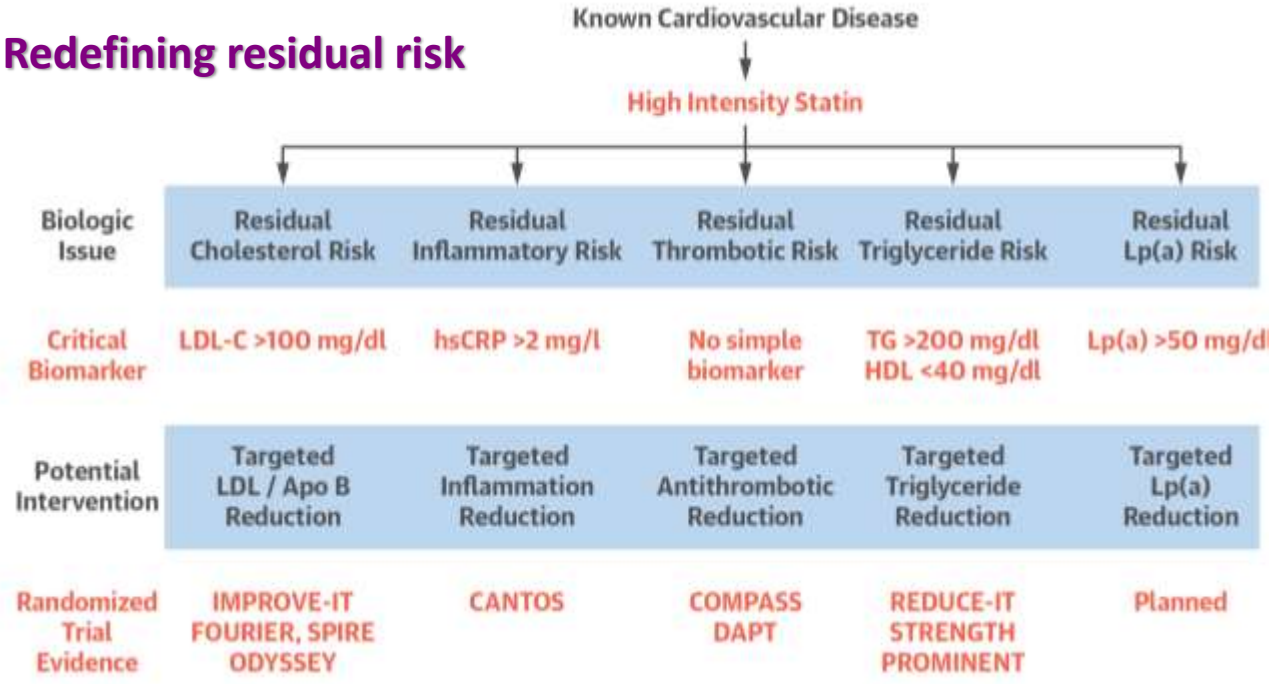
Prevenzione **PRIMARIA**

Residual risk and a movement toward personalized medicine



...patients remain at high residual risk for recurrent CV events for different underlying pathophysiologic reasons...

Redefining residual risk



Ridker, *J Am Coll Cardiol* 2018

Update on Cardiovascular Disease Risk in Patients with Rheumatic Diseases

Rheum Dis Clin N Am **2018**

Rachel H. Mackey, PhD, MPH[a,*], Lewis H. Kuller, MD, DrPH[b], Larry W. Moreland, MD[c]

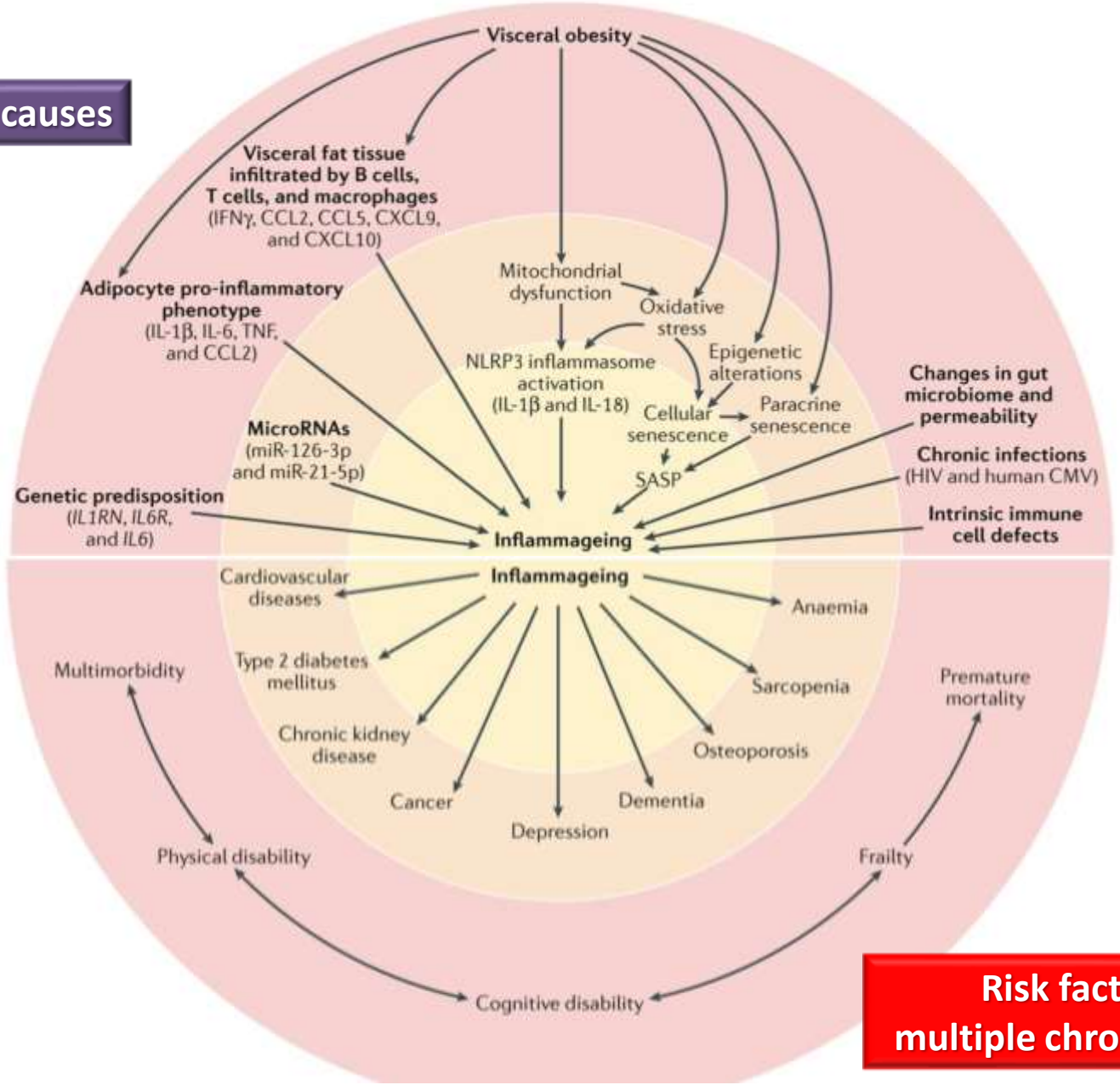
Cardiovascular disease risk factors in rheumatoid arthritis patients

KEY POINTS

- Cardiovascular disease (CVD) risk calculators underestimate CVD risk in rheumatoid arthritis (RA) and should be multiplied by 1.5 to reflect the greater than 1.5 times higher risk of CVD among adults with RA, even with no traditional CVD risk factors, although risk increases substantially with the number of CVD risk factors.
- Current CVD risk factors, particularly total and low-density lipoprotein (LDL)-C, likely underestimate the extent of subclinical atherosclerosis.
- LDL or high-density lipoprotein (HDL) particles, or apolipoprotein (apo)-B or ApoA1, may be more reliable CVD risk factors than cholesterol (total, LDL, or HDL) concentrations because of chronic inflammation.
- Reduction in inflammation may prevent or reduce myocardial injury and heart failure.
- Disease activity is a strong risk factor for CVD and mortality, and a key target for CVD risk reduction.

Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty

Potential causes



Risk factor for multiple chronic disease

Health Benefits of Exercise

Cold Spring Harb Perspect Med **2018**

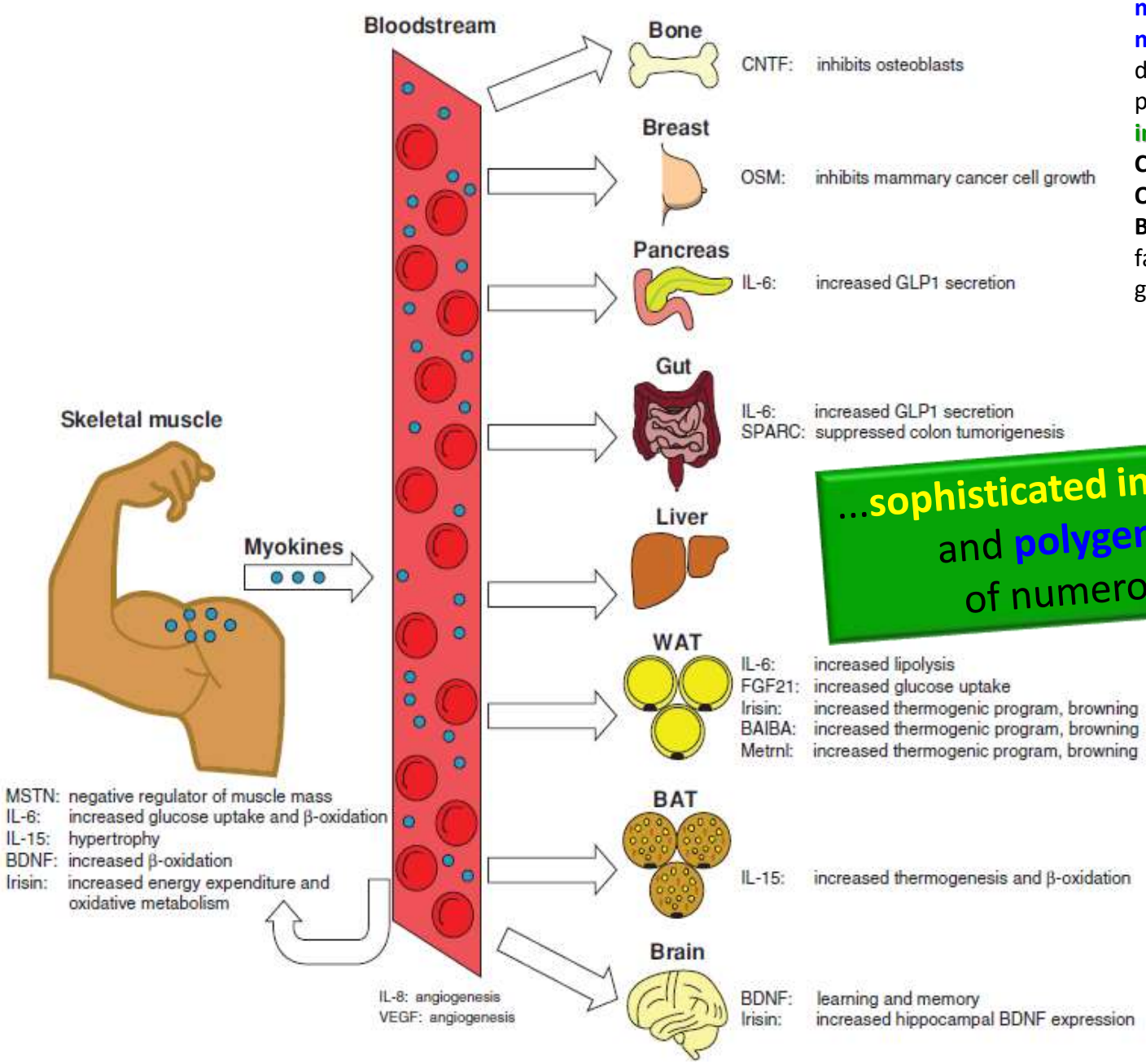
Gregory N. Ruegsegger[1] and Frank W. Booth[1,2,3,4]

There is arguably **no measure more important for health** than **cardiorespiratory fitness** (CRF) (commonly measured by maximal oxygen uptake, VO_2max)

Table 1. Worsening of 40 conditions caused by the lack of physical activity with growth, maturation, and aging throughout life span

1. Accelerated biological aging/premature death
2. Aerobic (cardiorespiratory) fitness (VO_{2max})
3. Arterial dyslipidemia
4. Balance
5. Bone fracture/falls
6. Breast cancer
7. Cognitive dysfunction
8. Colon cancer
9. Congestive heart failure
10. Constipation
11. Coronary (ischemic) heart disease
12. Deep vein thrombosis
13. Depression and anxiety
14. Diverticulitis
15. Endometrial cancer
16. Endothelial dysfunction
17. Erectile dysfunction
18. Gallbladder diseases
19. Gestational diabetes
20. Hemostasis
21. Hypertension
22. Immunity
23. Insulin resistance
24. Large arteries lose more compliance with aging
25. Metabolic syndrome
26. Nonalcoholic fatty liver disease
27. Obesity
28. Osteoarthritis
29. Osteoporosis
30. Ovarian cancer
31. Pain
32. Peripheral artery disease
33. Preeclampsia
34. Polycystic ovary syndrome
35. Prediabetes
36. Rheumatoid arthritis
37. Sarcopenia
38. Stroke
39. Tendons being less stiff
40. Type 2 diabetes

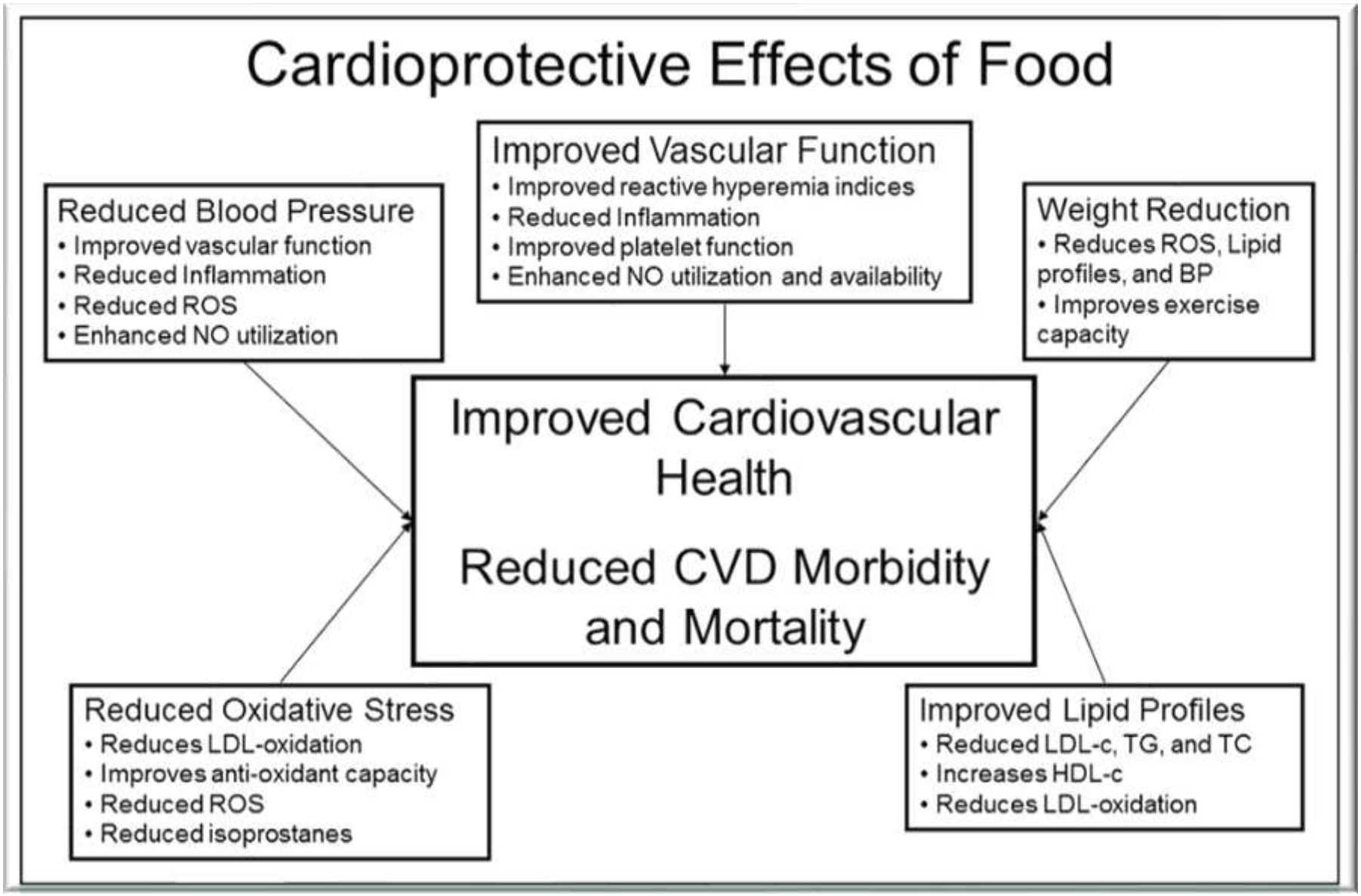
Figure provides an illustration of **myokine production by skeletal muscle** for actions within or at a distance. Myokine release promotes a **high degree of intertissue cross talk**.
CNTF, Ciliary neurotrophic factor; **OSM**, oncostatin M; IL, interleukin **BDNF**, brain-derived neurotrophic factor; **VEGF**, vascular endothelial growth factor



...**sophisticated interorgan cross-talk** and **polygenic integration** of numerous functions.

Ruegsegger & Booth, *Cold Spring Harb Perspect Med* 2018

The Mediterranean Diet, its Components, and Cardiovascular Disease



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Grazie per l'attenzione!

Dipartimento di Scienze Mediche
Università di Torino

e-mail: andrea.benso@unito.it

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